DELIVERED BY HAND ON JANUARY 13, 1999

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:
Pramod K. Srivastava

Application No.: 09/090,754 Group Art Unit: 1642

Filed: June 4, 1998 Examiner: G. Bansal

For: COMPOSITIONS AND METHODS FOR THE PREVENTION AND TREATMENT OF PRIMARY AND METASTATIC NEOPLASTIC DISEASES AND INFECTIOUS DISEASES WITH HEAT SHOCK/STRESS PROTEINS

Attorney Docket No.:8449-041

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination on the merits, please amend the above-identified application as follows. Applicant submits concurrently herewith: (a) a Fee Transmittal Sheet; (b) a Declaration under 37 C.F.R. § 1.68 and M.P.E.P. 608.01(p); and (c) an Associate Power of Attorney.

IN THE SPECIFICATION:

At page 4, line 23, delete "Kale", and insert in its place --Male--.

At page 7, line 17, delete "lifespan", and insert in its place --life span--.

At page 9, line 16, delete "after the primary".

At page 9, line 22, delete "test", and insert in its place --testes--.

At page 10, line 10, delete "closed", and insert in its place --cloned--.

At page 12, line 1, delete "hsp", and insert in its place --hsp-antigenic molecule complexes--.

At page 12, line 27, delete "to", and insert in its place --of--.

At page 13, lines 27-28, delete ", as described in legend to Fig. 1".

At page 14, line 14, delete "Figure 5. A. ADP-bound and ADP", and insert in its place --FIGS. 5A-B. FIG. 5A: ATP-bound and ATP--.

At page 14, line 15, after "found", insert --not--.

At page 14, line 15-16, delete "B. ATP-bound and ATP", and insert in its place --FIG. 5B: ADP-bound and ADP--.

At page 14, line 16, delete "not".

At page 15, line 17, delete "know", and insert in its place --known--.

At page 16, line 25, insert the following text:

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TABLE 1 Enzymes and chaperones that may be involved in protein folding and assembly in cells

Organism/organelle	Enzymes			Chaperones		
Protein family	PDI	Cyclophilin PPIase	FKBP PPIase	Hsp60 (Chaperonin-60)	Hsp70 (Stress-70)	Hsp90 (Stress-90)
E. coli						
Cytosol	Thioredoxin	PPIase b		GroEL	DnaK	HtpG (C62.5)
Periplasm		PPIase a (Rotamase)				
Yeast						
Cytosol		Cph1p (Cpr1p)	Fkb1p (Fkr1p) (Rbp1p)		Ssa1-4p	Hsp83 Hsc83
ER	PDI Eug1p	yCyPB			Kar2p (BiP)	
Mitochondria				Hsp60 (Mif4p)	Ssc1p	
Drosophila						
Cytosol		CyP			Hsp68 Hsp70 Hsc1,2,4	Hsp83
ER	PDI	NinaA				
Mammals						
Cytosol		Cyclophilin (PPIase) (CyPA)	FKBP		Hsp70(p73) Hsc70(p72) (CUATpase) (Prp73)	Hsp90 (Hsp83) (Hsp87)
ER	PDI (ERp59) GSHP ERp72 ERp61	CyPB (rCyPLP)			BiP (Grp78)	Grp94 (ERp99) (endoplasmin)
Mitochondria				Hsp60 (Hsp58)	Hsp70 (Grp75)	
Plants						
Cytosol						
ER	PDI				b70(BiP)	
Chloroplasts				RuBP		

Six protein families have been identified whose members include enzymes or chaperones proposed to be involved in folding, assembly, rearrangement or degradation of proteins in cells. Members that have been characterized to date from a variety of different organisms are shown. Alternative names are shown in parenthesis.

The *S. cerevisiae* genome contains at least nine genes related to *HSP70* of higher eucaryotes. Eight of these genes, originally named *TG100-YG107*, have been renamed on the basis of structural and functional similarities: SSA1-4 (stress seventy family *A*; *YG100*, *YG102*, *YG106*, *YG107*,

respectively); *SSB1* AND *SSB2* (YG101 and YG103, respectively); *SSC1* (*YG104*); and *SSD1* (*YG105*).--

At page 16, line 27, after "have", insert --not--.

At page 20, line 21, delete "1", and insert in its place --2--.

At page 28, line 37, delete "oxtyl", and insert in its place --octyl--.

At page 30, line 3, delete "know", and insert in its place --known--.

At page 30, line 29, delete "trifluoro acetic" and insert in its place --trifluoroacetic--.

At page 30, line 32, after "minutes", insert --resulting in eluted denatured peptide and denatured stress protein--.

At page 31, lines 8-9, after "(HPLC)" delete "T"; and delete "VYDAC", and insert in its place --VYDAC™ (Separations Group, Inc., Hesperia, CA)--.

At page 36, line 31, after "for 1 hr.", insert --, thereby forming an ADP-hsp70-peptide complex--.

At page 37, line 8, delete "target", and insert in its place --tumor--.

At page 37, line 18, delete "target", and insert in its place --tumor--.

At page 38, line 20, delete "paletted", and insert in its place --pelleted--.

At page 42, line 27, delete "fungi", and insert in its place --fungi,--.

At page 47, line 27, delete "irradiate", and insert in its place --eradicate--.

At page 49, line 5, delete "hsp", and insert in its place --hsps and--.

At page 50, line 25, delete "shorted", and insert in its place --shortly--.

At page 50, line 25, delete "need", and insert in its place --needle--.

At page 50, line 33, delete "test", and insert in its place --concentration--.

At page 51, line 4, delete "centrifigation", and insert in its place --centrifugation--.

At page 53, line 10, delete "6138", and insert in its place --UV6138--;

At page 53, line 11, delete "6139ST", and insert in its place --UV6139SJ--;

At page 53, line 12, delete "6138", and insert in its place --UV6138--;

At page 53, line 13, delete "6139SJ", and insert in its place --UV6139SJ--.

At page 54, line 9, delete "UV6139", and insert in its place --UV6139SJ--.

At page 54, line 9, delete "UV6139 SJ", and insert in its place --UV6139S--.

At page 57, line 20, delete "MCTCs", and insert in its place --MLTCs--.

At page 57, line 27, delete "bene", and insert in its place --been--.

At page 58, line 24, delete "regiment", and insert in its place --regimen--.

At page 59, line 16, delete "e0", and insert in its place --e)--.

At page 60, line 22, after "with peptides", insert -- (*i.e.*, the hsp70 preparation was an ADP-hsp70-peptide complex)--.

At page 60, line 25, delete ". (Figures 5A and 5B)", and insert in its place --(Figures 5B and 5A, respectively)--.

IN THE CLAIMS:

Please add new claims 62-77, as follows:

62. (New) A method for purifying heat shock protein 70 complexes comprising the steps of:

adding a solution containing a heat shock protein complex comprising a heat shock protein associated with at least one member of the group consisting of peptides, polypeptides, denatured proteins and antigens associated therewith to an ADP matrix column containing an ADP matrix to bind the heat shock protein complexes to the ADP matrix; and

adding a buffer containing ADP to the column to remove the heat shock protein complexes in an elution product.

63. (New) The method of Claim 62 wherein the solution containing heat shock protein complexes comprises a cell lysate.

64. (New) The method of Claim 62 wherein the heat shock protein complexes include complexes in which the heat shock protein comprises one of the group consisting of DnaK proteins from prokaryotes; Ssa, Ssb, and Ssc from yeast; hsp70, Grp75 and Grp78(Bip) from eukaryotes.

65. (New) A method for synthesizing heat shock protein 70 complexes, comprising adding a heat shock protein and an antigenic molecule selected from the group consisting of peptides, polypeptides, denatured proteins, and antigens to a buffer containing ADP to allow the heat shock protein 70 to bind to the antigenic molecule and ADP to form a heat shock protein 70 complex.

66. (New) The method of Claim 65, wherein the solution containing the heat shock protein 70, antigenic molecule and ADP is incubated at 37° C to induce heat shock protein 70 present in the solution to bind to peptides, polypeptides, denatured proteins and antigens present in the solution to form heat shock protein 70 complexes.

67. (New) The method of Claim 65, wherein the heat shock protein 70 comprises one of the group consisting of DnaK proteins from prokaryotes; Ssa, Ssb, and Ssc from yeast; hsp70, Grp75 and Grp78(Bip) from eukaryotes.

68. (New) An ADP-heat shock protein 70-peptide complex in substantially purified form.

69. (New) The ADP-heat shock protein 70-peptide complex of Claim 68, wherein said heat shock protein 70 comprises one of the group consisting of DnaK proteins from prokaryotes; Ssa, Ssb, and Ssc from yeast; hsp70, Grp75 and Grp78(Bip) from eukaryotes.

70. (New) The ADP-heat shock protein 70-peptide complex of Claim 68, wherein said peptide comprises one of the group consisting of polypeptides and proteins.

71. (New) The ADP-heat shock protein 70-peptide complex of Claim 68, wherein said ADP-heat shock protein 70-peptide complex comprises a synthetic heat shock protein-peptide complex.

72. (New) The ADP-heat shock protein-peptide complex of Claim 71, wherein said synthetic heat shock protein-peptide complex comprises a heat shock protein and a peptide from the same individual.

73. (New) The ADP-heat shock protein-peptide complex of Claim 71, wherein said synthetic heat shock protein-peptide complex comprises a heat shock protein from a first individual and a peptide from a second, different individual.

74. (New) The ADP-heat shock protein-peptide complex of Claim 71, wherein said synthetic heat shock protein-peptide complex comprises a heat shock protein from a first organism and a peptide from a second organism.

75. (New) The ADP-heat shock protein-peptide complex of Claim 71, wherein said synthetic heat shock protein-peptide complex comprises a heat shock protein from a first species and a peptide from a second species.

76. (New) The ADP-heat shock protein-peptide complex of Claim 68, wherein the ADP-heat shock protein-peptide complex is purified by the steps of:

adding a heat shock protein complex comprising a heat shock protein associated with at least one member of the group consisting of peptides, polypeptides, denatured proteins and antigens associated therewith to ADP matrix column containing an ADP matrix to bind the heat shock protein complexes to the ADP matrix; and

adding a buffer containing ADP to the column to remove the heat shock protein complexes in an elution product.

77. (New) The ADP-heat shock protein-peptide complex of Claim 68, wherein the ADP-heat shock protein-peptide complex is synthesized by adding a heat shock protein and an antigenic molecule selected from the group consisting of peptides, polypeptides, denatured proteins, and antigens to a buffer containing ADP to allow the heat shock protein 70 to bind to

the antigenic molecule and ADP to form a heat shock protein 70 complex.

REMARKS

The specification has been amended, in part, to correct minor typographical or editorial errors. No new matter has been introduced.

Specifically, "VYDAC" at page 31 has been properly identified as a trademark and its source has been indicated, Separations Group, Inc. inherently being the owner of such registered trademark and, thus, the source of the product.

Support for the amendment at page 37, lines 8 and 18, with respect to mixed lymphocyte tumor cell assay, can be found, for example at page 55, line 16.

Support for the amendments, at pages 14 and 60, to the references to Figures 5A and 5B, which were inadvertently reversed, can be found, for example in the figures themselves. In particular, Figure 5A contains a reference to ATP in the text above the graph, and Figure 5B contains a reference to ADP in the text above the graph. Moreover, it would be readily apparent to one of ordinary skill in the art the graph in Figure 5B indicates the association of peptides with heat shock protein 70 (ADP-bound and ADP eluted), whereas Figure 5A indicates, in comparison, a lack of association of peptides with heat shock protein 70 (ATP-bound and ATP eluted).

Support for the amendments at pages 53 and 54 regarding UV6139SJ cells can be found, for example, in at page 13, line 3; and page 54, lines 4 and 5.

The specification has been amended at page 16, line 25 to replace material incorporated by reference with actual text referred to, in accordance M.P.E.P 2163.07(b) and 608.01(p). No new matter has been introduced. More specifically, Gething, et al., 1992 *Nature* 355:33-45 (a copy of which is attached hereto as Exhibit A); and Lindquist, et al., 1988, *Annu. Rev. Genetics* 22:631-677 (a copy of which is attached hereto as Exhibit B) were each incorporated by reference at page 16, lines 19-21 of the specification with respect to the preceding description, at page 16, lines 6-16, of the members of hsp60, hsp70, and hsp90 families of proteins. Accordingly, the actual text of Table 1 at page 35 of Gething et al., which describes various family members of each of these protein families, has been included in the specification. In addition, the actual text of the first two sentences below the heading "*Saccharomyces cerevisiae*" at page 642, lines 5-10 of Lindquist et al., which describes the genes encoding the members of the hsp70 protein family in *Saccharomyces cerevisiae*, has been included in the specification.

Applicant submits herewith a Declaration under 37 C.F.R. § 1.68 and M.P.E.P. 608.01(p) which states that the amendatory material that was included in the specification at page 16, line 25 consists of the same material incorporated by reference in the application as filed at page 16, lines 19-21.

The name of the table at page 20, line 21 of the specification as filed has been changed from Table 1 to Table

2 to reflect the inclusion of the actual text of Table 1 from Gething et al. at page 16, line 25, as set forth above.

The specification has been amended at page 30, line 32 to recite an inherent property of the methods described at page 30, lines 28-34, in accordance with M.P.E.P. 2163.07(a). *See In re Reynolds*, 443, F.2d 384, 170 USPQ 94 (CCPA 1971); *In re Smythe*, 480 F.2d 1376, 178 USPQ 279 (CCPA 1973). More specifically, the methods described at page 30, lines 28-34 inherently produce denatured products. Thus, no new matter has been introduced.

The specification has been amended at page 36, line 31, and at page 60, line 22, to recite an inherent property of the complex produced by the methods described at page 36, lines 25-32, and at page 60, lines 4-23, respectively, in accordance with M.P.E.P. 2163.07(a). *See In re Reynolds*, 443, F.2d 384, 170 USPQ 94 (CCPA 1971); *In re Smythe*, 480 F.2d 1376, 178 USPQ 279 (CCPA 1973). More specifically, the methods described at page 36, lines 25-32, and at page 60, lines 5-25 inherently produce ADP-hsp70-peptide complexes. Thus, no new matter has been introduced.

Claims 60-77 are currently pending, new Claims 62-77 having been added in the present amendment. New Claims 62-77 are completely supported in the specification, and no new matter has been introduced.

Support for new Claim 62 can be found, for example, at page 25, lines 1-17; in Section 9 (page 60, lines 5-35), in Figures 5A and 5B; page 32, line 8 (with respect to polypeptides); page 10, line 17; page 22, line 30 to page 23,

line 4; page 30, lines 28-34 in the specification as filed and the text that was inserted at page 30, line 32 by the amendment above (with respect to denatured proteins); and page 33, line 5 (with respect to antigens).

Support for new Claim 63, with respect to a cell lysate, can be found, for example, at page 60, line 14.

Support for new Claims 64, 67,and 69, with respect to the specified members of the hsp70 family, can be found for example at page 16, lines 8-24; page 16, line 36 to page 17, line 18; and by the text from Gething, et al., 1992 *Nature* 355:33-45, and Lindquist, et al., 1988, *Annu. Rev. Genetics* 22:631-677, which was included in the specification by virtue of the amendment at page 16, line 25 set forth above.

Support for new Claim 65 can be found, for example, at page 36, lines 25-32; page 29, line 28 (with respect to peptides); page 10, line 17; page 22, line 30 to page 23, line 4; page 32, line 8 (with respect to polypeptides); page 30, lines 28-34 in the specification as filed and the text that was inserted at page 30, line 32 by the amendment above (with respect to denatured proteins); and page 33, line 5 (with respect to antigens).

Support for new Claim 66 can be found, for example, at page 36, line 30.

Support for new Claim 68 can be found, for example, at page 25, lines 1-17; in Section 9 (page 60, lines 5-35 of the specification as filed and the text that was inserted at page 60, line 22 by the amendment above); in Figures 5A and 5B; and page 36, lines 25-32 in the specification as filed and

the text that was inserted at page 36, line 31 by the amendment above, which describe substantially purified ADP-hsp70-peptide complexes and methods for producing such complexes.

Support for new Claim 70, with respect to polypeptides and proteins, can be found throughout the specification, including, for example, page 10, line 17; page 22, line 30 to page 23, line 4; and page 32, line 8.

Support for new Claim 71, with respect to a synthetic heat shock protein-peptide complex, can be found, for example at page 36, lines 25-32.

Support for new Claims 72 and 73, with respect to the sources of the heat shock protein and the peptide, can be found, for example, at page 10, lines 8-11; and page 35, line 25 to page 36, line 1.

Support for new Claims 74 and 75, with respect to the sources of the heat shock protein and the peptide, can be found, for example, at page 10, lines 8-11; page 15, line 31; page 29, lines 17-24; page 30, lines 6-12; throughout Section 5.2.5 (page 33, line 4 to page 35, line 22); and page 35, line 25 to page 36, line 1.

Support for new Claim 76 can be found, for example, at page 25, lines 1-17; in Section 9 (page 60, lines 5-35 of the specification as filed and the text that was inserted at page 60, line 24 by the amendment above); and in Figures 5A and 5B; which describe substantially purified ADP-hsp70-peptide complexes and methods for producing such complexes.

Support for new Claim 77 can be found, for example, at page 36, lines 25-32 in the specification as filed and the

text that was inserted at page 36, line 31 by the amendment above, which describe substantially purified ADP-hsp70-peptide complexes and methods for producing such complexes.

Applicant respectfully requests that the above-made amendments and remarks be entered and made of record in the file history of the instant application.

Respectfully submitted,

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Date: January 13, 1999

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